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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,692	11/16/2000	Kuo-Fen Lee	D6233CIP	5372

7590 03/20/2002

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	9

DATE MAILED: 03/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/714,692	LEE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 24-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-27* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 12 February 2002 (Paper No. 8) has been entered in full. Claims 20 and 21 are amended.

This application contains claims 1-19 and 24-27 drawn to an invention nonelected without traverse in Paper No. 4 (28 June 2001). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 20-23 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 2-3 of the previous Office Action (Paper No. 5, 13 August 2001) are *withdrawn in part* in view of the amended title and amended description of Figure 6 (Paper No. 8, 12 February 2002). See section on Specification, below.

2. The rejections to claims 20-23 under 35 U.S.C. 112, second paragraph, as set forth at pg 5 of the previous Office Action (Paper No. 5, 13 August 2001) are *withdrawn* in view of the amended claims (Paper No. 8, 12 February 2002).

Specification

3. The Brief Description of the Drawings for Figure 1D refers to staining in the cortex, symbolized as (C) on the Figure. However, the letter (C) is not visible on Figure 1D. The basis for this objection is set forth at pg 2 of the previous Office Action (Paper No. 5, 13 August

2001). Applicant asserts that a new Figure 1D that has a visible letter "C" is submitted. Applicant's argument has been fully considered but not found to be persuasive because a new Figure 1D was not submitted with the amendment of 12 February 2002 (Paper No. 8).

4. The amendment filed 12 February 2002 (Paper No. 8) is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows. Applicant has introduced new matter in the amended Brief Description of Figures for Figures 4A-H. Specifically, the amended description of Figures 4A and 4C describe the graphical results of experiments performed with male mice while the amended description of Figures 4B and 4D describe the graphical results of experiments performed with female mice. However, the specification does not disclose that the experiments were performed according to mouse gender (pg 33-37). Furthermore, the specification neither describes any of the results of Figures 4E-4H nor refers to Figures 4E-4H.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112, first paragraph

5. Claims 20-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 20-23 are directed to a method of inhibiting angiogenesis in a target tissue comprising administering a Corticotropin Releasing Factor Receptor 2 (CRFR2) agonist to an individual having a pathophysiological condition selected from the group consisting of cancer

and diabetic retinopathy. The claims also recite that the CRFR2 agonist is selected from the group consisting of urocortin and CRF and the target tissue is selected from the group consisting of heart, brain, pituitary, gonad, kidney, adipose, and gastrointestinal tract tissues. The basis for this rejection is set forth for claims 20-23 at pg 3-5 of the previous Office Action (Paper No, 5, 13 August 2001).

Applicant's arguments (Paper No. 8, 12 February 2001), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the present invention provides data that indicate CRFR2 null mutant mice exhibit an increase in the size and number of blood vessels in various tissues. Applicant contends that since CRFR2 receptor and its activity have been localized within the endothelial cell layer of blood vessels, Applicant's data indicates that CRFR2 plays a significant role in regulating angiogenesis. Applicant argues that one of ordinary skill in the art would conclude that well-known CRFR2 agonists such as urocortin and CRF could be used to inhibit angiogenesis.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the specification of the instant application does not disclose the identity of any CRFR2 agonist capable of inhibiting angiogenesis in any target tissue in any subject with any pathophysiological condition. The specification outlines a prophetic procedure for inhibition of angiogenesis in a target tissue by administration of a CRFR2 agonist (pg 8, lines 6-10; pg 25, lines 19-21; pg 26, lines 1-4). However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The claimed method may not necessarily inhibit angiogenesis in a target tissue.

Although the specification discloses that agonists such as urocortin or CRF could be utilized in the claimed method, the skilled artisan must resort to trial and error experimentation to determine the optimal route of administration of the agonist, as well as the quality and duration of treatment in a subject. Such trial and error experimentation is considered undue.

(ii) Applicant disagrees with Examiner's cited reference of Griffieon et al. Applicant does not agree that many anti-angiogenic therapies, particularly for treating cancer, were highly active in animal models. Applicant argues that tumor angiogenesis is essential for the growth of primary and metastic tumors. Applicant states that for tumors to create a neovascular blood supply, tumor cells need to secrete proangiogenic factors in order to overcome the inhibitory angiogenic factors. Applicant also asserts that Griffioen et al. is not referring to common methodologies of drug treatment, such as IV infusion that are well known in the art and do not require any special skills to practice. Applicant indicates that for treatment of cardiovascular disease, one of ordinary skill in the art would readily employ methods of local transfer since local transfer of an agent by perivascular or intravascular delivery provides a way of enhancing arterioprotective endothelial functions without stimulating neovascularization at other sites.

Applicant's arguments have been fully considered but are not found to be persuasive. The citation of Griffieon et al. (Pharmacol Rev 52(2): 237-268, 2000) in the previous Office Action was to indicate the state of the art at the time the invention was made. Griffieon et al. review some of the challenges encountered with anti-angiogenic therapies and state that anti-angiogenic therapy results to date have been disappointing (pg 260-262). Therefore, the skilled artisan would not necessarily be able to predict that administration of a CRFR2 agonist by any

technique would inhibit angiogenesis in a tissue. Although Griffieon et al. do not specifically refer to the success or failure of general types of administration methodologies, Griffieon et al. emphasize that strategies to target stages of disease progression require preclinical research effort on formulations, dosing regimens, etc. Furthermore, the claims and the specification of the instant application do not recite a particular methodology of CRFR2 agonist administration. Undue experimentation would be required of the skilled artisan to determine the optimal route of agonist administration in an individual.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to inhibit angiogenesis by administration of a CRFR2 agonist and to determine the route, quantity, and duration of administration of the agonist, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art (see Griffioen et al.), and the unpredictability of the effects of a CRFR2 agonist on angiogenesis inhibition, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

Bridget E. Bunner
Art Unit 1647
March 7, 2002

ELIZABETH KEMMERER
PRIMARY EXAMINER